AD_____

Award Number: DAMD17-00-1-0198

TITLE: Genetics of Breast Cancer in Blacks

PRINCIPAL INVESTIGATOR: Olufunmilayo I. Olopade, M.D.

CONTRACTING ORGANIZATION: The University of Chicago
Chicago, Illinois 60637

REPORT DATE: September 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2002	Annual (1 Sep 01 - 31 Aug 02)

4. TITLE AND SUBTITLE
Genetics of Breast Cancer in Blacks

5. FUNDING NUMBERS
DAMD17-00-1-0198

6. AUTHOR(S) :
Olufunmilayo I. Olopade, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Chicago
Chicago, Illinois 60637

E-Mail: folopade@medicine.bsd.uchicago.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Breast cancer in these young Black women is more virulent, leading to a decrease in the overall survival rates for African Americans diagnosed with breast cancer when compared to Whites. Our studies involve a new approach that involves large numbers of breast cancer patients from Africa and provide the first concerted effort to seriously address the contribution of genetic risk factors to the high incidence and mortality from breast cancer in young Black women. We have developed an efficient mechanism to recruit incident cases of early onset breast cancer, with the goal of enrolling 75-100 new cases per year from Nigeria and 50-75 cases per year in the US. We have used the *Chronic Disease Network*-- a collaborative framework for the study of international comparisons among black populations to develop this infrastructure and we are now awaiting approval of our clinical protocol by the Human Subject Review Committee. We have finalized the instruments to be used, and completed our training in Nigeria. In the next year, we will optimize our mutation detection assay using Denaturing High Performance Liquid Chromatography. We will recruit and analyze 200 U.S Black women diagnosed with breast cancer at, or before, age 40, for *BRCA1* and *BRCA2* mutations and compare the incidence and spectrum of mutations to that seen in a matched cohort of African women. Comparisons will be made to published literature in White women.

14. SUBJECT TERMS:	15. NUMBER OF PAGES
breast cancer, African Americans, women, genetics	5
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

ABSTRACT

Breast cancer in these young Black women is more virulent, leading to a decrease in the overall survival rates for African Americans diagnosed with breast cancer when compared to Whites. Our studies involve a new approach that involves large numbers of breast cancer patients from Africa and provide the first concerted effort to seriously address the contribution of genetic risk factors to the high incidence and mortality from breast cancer in young Black women. We have developed an efficient mechanism to recruit incident cases of early onset breast cancer, with the goal of enrolling 75-100 new cases per year from Nigeria and 50-75 cases per year in the US. We have used the *Chronic Disease Network*-- a collaborative framework for the study of international comparisons among black populations to develop this infrastructure and we are now awaiting approval of our clinical protocol by the Human Subject Review Committee. We have finalized the instruments to be used, and completed our training in Nigeria. In the next year, we will optimize our mutation detection assay using Denaturing High Performance Liquid Chromatography. We will recruit and analyze 200 U.S Black women diagnosed with breast cancer at, or before, age 40, for *BRCA1* and *BRCA2* mutations and compare the incidence and spectrum of mutations to that seen in a matched cohort of African women. Comparisons will be made to published literature in White women.

INTRODUCTION

Breast cancer is a major health problem in the Western world and the leading cause of death among American women 40-55 years of age. Among women born and raised in the US, African-American women have a lower risk of breast cancer than white women, but the survival of AA women following diagnosis is poorer. It has been observed that the age distribution of disease onset as well as tumor histology is different between Caucasian and African-American patients. African-American patients have a greater incidence between 30-44 years, and medullary carcinoma is more frequent in AA patients. The greater percentage of African-American women than Caucasian women diagnosed with breast cancer under age 50 suggests a genetic contribution to breast cancer in African-American women. However, very few data are available from this population to evaluate this possibility. There are not even adequate data to determine whether racial differences exist in the familial clustering of breast cancer.

With the identification of *BRCA1* and *BRCA2*, it should now be possible to study the genetics of breast cancer in Africans and African-Americans. Although a challenging task, we can now track ancient mutations to Africa and one such mutation in *BRCA1*-926ins10 has been identified in families from Florida, Washington, the Bahamas, and Ivory Coast. Studies of populations with ancient *BRCA1* and *BRCA2* mutations may also reveal environmental causes and other genes that modify inherited risk. For example *BRCA1* 185delAG is found at approximately equal frequencies in Iraqi/Iranian and Ashkenazi Jewish families (0.5% and 1.0% frequencies respectively), yet breast and ovarian cancer rates are significantly lower among Iraqi/Iranian than among Ashkenazi Jewish women.

This proposal is novel in that it will include women from West Africa, the founder population for almost all African-Americans. It will provide the first concerted effort to seriously address the contribution of genetic risk factors to the high incidence and mortality from breast cancer in young African American women.

BODY

Task 1: To develop mechanisms to recruit incident cases of early onset breast cancer, with the goal of enrolling 75-100 new cases per year from Nigeria and 50 cases per year in the US. The goal of this Idea grant is to determine the feasibility of using the *CDN* to develop the infrastructure necessary for comparative studies of breast cancer involving Nigeria in West Africa, the Caribbean and the US. The initial phase will involve investigators in the US and Nigeria.

Progress: We have establish procedures at both sites, finalized the questionnaires, organized staff and established data management and communications mechanisms. Unfortunately, there was significant delay in the approval of our Human Subjects protocol. Despite having organized training workshops in Nigeria with our support staff, we ca no longer recruit the Nigerian cases. Rather we will devote our energies into recruiting the cases in the US. We applied to the National Cancer Institute based on our preliminary work in Nigeria and have now received funding for 5 years to extend this work in Nigeria.

Task II: To describe the contribution of mutations in *BRCA1* and *BRCA2* to early onset breast cancer in African-Americans. For this aim, we will analyze 200 African-American women diagnosed with breast cancer at, or before, age 40, for *BRCA1* and *BRCA2* mutations, and compare the incidence and spectrum of mutations to that seen in a matched cohort of African women. Along with the molecular analysis, we will collect detailed family cancer history information on each participant to determine whether differences exist in clustering of breast and other cancers in the families of young women with breast cancer, in the United States. Kindreds that are segregating a mutation will be extended and characterized for age-specific penetrance, risks of other cancers, and epidemiologic risk factors.

Progress: BRCA1/2 mutation detection in a large cohort requires automated, high-throughput methodology that does not compromise sensitivity. In our experience and that of other labs, the most sensitive and efficient method for detecting mutations prior to sequencing is denaturing high performance liquid chromatography (DHPLC). Using known mutations from our clinical samples and a blinded set of 22 genomic samples provided by Coriell, we have worked out conditions for mutation detection in BRCA1 using the WAVE (Transgenomic) DHPLC system in collaboration with Dr. Soma Das. 35 PCR reactions are used to amplify all BRCA1 exons, including flanking intron/exon boundaries. Amplification is followed by denaturation and slow cooling to generate heterodulex molecules, which are injected into alkylated nonporous polystyrene-divinylbenzene (PS-DVB) copolymer DHPLC columns and eluted with an acetonitrile gradient. Eluted fragments are detected by automated spectrophotometry and results are analyzed using WaveMaker™ software. Automation allows the injections and elutions at several temperatures, which maximizes the sensitivity of heteroduplex detection. Once heteroduplex molecules are identified, candidate exons are sequenced to identify the mutation. This year, we completed our analysis of the 22 Blinded mutant samples and successfully identified all the mutations in the blinided samples. Our experience with DHPLC analysis of BRCA1 mutations is similar to other labs, and we anticipate complete BRCA1 and BRCA2 analysis of the breast cancer patient samples once we complete our accrual in the next year.

KEY RESEARCH ACCOMPLISHMENTS:

Too early to report. We have just received IRB approval for our Human subject recruitment.

REPORTABLE OUTCOMES:

N/A

CONCLUSIONS:

N/A Too early

REFERENCES: None

APPENDICES: None

BINDING: Because all reports are entered into the Department of Defense Technical Reports Database collection and are microfiched, it is recommended that all reports be bound by stapling the pages together in the upper left hand corner. All reports shall be prepared in camera ready copy (legible print, clear photos/illustrations) for microfiching. Figures should include legends and all figures and tables should be clearly marked.